



Diuretic strategies in acute decompensated heart failure

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Abstract

Hospitalization for ADHF is linked to poor outcomes, with residual congestion at discharge significantly increasing the risk of HF readmissions and mortality. Diuretic resistance is a major contributor to inadequate decongestion during ADHF treatment. In this review, we discuss various decongestive strategies, emphasizing the management of diuretic resistance. Additionally, we examine the limitations of current decongestion trials and highlight key priorities for future research.

Keywords Diuretic resistance · ADHF · Neurohormonal activation

Background

Inadequate decongestion during hospitalization for acute decompensated heart failure (ADHF) is linked to higher rates of readmission and mortality [1, 2]. However, despite efforts to achieve decongestion, approximately one-third of patients are discharged with residual volume overload [1, 2]. Challenges in assessing volume overload at the bedside, along with comorbidities that contribute to diuretic resistance, are among the key factors that may impede effective decongestion (Table 1). Many signs and symptoms of congestion lack sufficient sensitivity and specificity, complicating the assessment of volume status [3]. Diuretic resistance, particularly common in patients with concomitant chronic kidney disease (CKD), limits the efficacy of loop diuretics and poses a significant barrier to achieving adequate decongestion [4]. In this review, we will examine medical decongestive strategies in patients with ADHF, with a particular focus on diuretic resistance.

Loop diuretic therapy

Loop diuretics, such as furosemide, bumetanide, and torsemide, work by inhibiting the apical sodium–potassium–chloride co-transporter in the thick ascending loop of Henle where 20–25% of filtered sodium is reabsorbed. Historically,

loop diuretics have been the mainstay of both chronic and acute HF treatment, despite a lack of objective evidence demonstrating that they improve long-term outcomes in HF. For patients with ADHF, rapid administration of intravenous (IV) loop diuretics is recommended [5–7], except in cases of cardiogenic shock or isolated right ventricular failure. In patients on chronic diuretic therapy, expert consensus statements recommend an initial IV diuretic dose 1–2.5 times the calculated daily dose of oral furosemide (Table 2) [5]. This dosing regimen is based on the Diuretic Optimization Strategies in Acute Heart Failure (DOSE-AHF) trial, which utilized a 2 × 2 factorial design to compare bolus vs. continuous infusion and high (2.5x) vs. low (1x) dose IV furosemide in patients with ADHF [8] (Table 3). The trial found no significant difference between bolus and continuous infusion strategies, but high-dose IV furosemide was more effective than low-dose in promoting diuresis and alleviating symptoms within 72 h, without significant differences in kidney function.

The choice of IV loop diuretic therapy may be influenced by pharmacodynamic differences between agents (Table 2) [4, 9–11], but no trials have directly compared the efficacy of different IV loop diuretics in ADHF. Overall, there is no clear “best choice” among loop diuretics for the treatment of HF.

Diuretic resistance

Diuretic resistance occurs when escalating diuretic doses fail to achieve adequate decongestion [4]. Mechanisms of diuretic resistance can be broadly classified as pre-renal and intra-renal. Pre-renal factors include hemodynamic

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Table 1 Potential reasons for inadequate decongestion during treatment for acute decompensated heart failure

1	Inadequate background guideline-directed medical therapy
2	Limitations in bedside assessment of volume overload
3	Underlying comorbidities (e.g., obesity, pulmonary hypertension, chronic kidney disease) that complicate fluid management
4	Diuretic resistance
5	Advanced heart failure
6	Poor nutritional and functional status
7	Inadequate monitoring of diuretic response/escalation of therapy
8	Financial and patient pressures to limit length of stay

References: 4, 6, 8, 9

derangements such as venous congestion, increased intra-abdominal pressure, and reduced cardiac output, which can lead to decreased renal blood flow and diuretic delivery to the kidney [4, 10]. Other pre-renal mechanisms include hypoalbuminemia which increases diuretic volume of distribution, leading unbound diuretics to diffuse outside the intravascular space instead of being delivered to the tubules [4, 12]. Several intra-renal mechanisms also contribute to diuretic resistance. Neurohormonal activation, such as angiotensin II upregulation, increases sodium reabsorption in the proximal tubule and is particularly dysregulated in ADHF [4, 13]. In CKD, increased organic anions and urate compete with loop diuretics for proximal tubular secretion, preventing them from reaching the loop of Henle and reducing their effectiveness [4, 10]. CKD itself, with its low glomerular filtrate rate (GFR), diminishes the filtered load of sodium making natriuresis challenging and sometimes necessitating multiple daily diuretic doses [4]. Hypochloremia, often due to loop diuretics, is linked to diuretic resistance in HF [14]. Hypochloremia leads to upregulation of the sodium–potassium-chloride co-transporter (NKCC) and antagonizes the effect of loop diuretics by promoting sodium reabsorption in the loop of Henle [15]. Metabolic alkalosis indirectly reduces luminal chloride, stimulating aldosterone and increasing sodium and chloride reabsorption in the distal tubule [4, 10]. Additionally, chronic diuretic use induces neurohormonally mediated hypertrophy and hyperplasia of the distal nephron, increasing sodium and chloride reabsorption through the sodium chloride co-transporter in the distal tubule (NCC) and sodium reabsorption through the epithelial sodium channels (ENAC) in the collecting ducts [4, 10].

Sodium avidity in HF

In HF, the proximal tubule is the major site of sodium reabsorption, facilitated by several sodium transporters and the sodium potassium ATPase pump [16]. Passive water

absorption occurs alongside sodium reabsorption via the peritubular capillaries [16]. HF exacerbates this sodium avidity, especially in cases of reduced renal blood flow. Increased filtration fraction, needed to maintain GFR, raises peritubular capillary oncotic pressure, further promoting sodium reabsorption [4]. Renal venous congestion also increases pressure within the tubular lumen, further enhancing sodium reabsorption [17]. Lastly, increased interstitial pressure from venous congestion can lead to lymphatic washout of proteins, decreasing interstitial oncotic pressure and increasing sodium reabsorption [4]. Recognizing and addressing these mechanisms is crucial for managing sodium avidity and diuretic resistance in HF.

Early recognition of diuretic resistance and spot urine sodium

Markers of diuretic response, such as urine volume and natriuresis, are crucial for assessing decongestion (Table 4). A small study found that an impaired natriuretic response (urinary sodium < 50 mEq/L) was associated with lower weight loss and less net fluid output over 24 h of continuous IV furosemide [18]. A correlation was established between spot urine levels (measured 2 h after diuretic administration) and subsequent natriuresis (within 6 h of diuretic administration). This led to the development of a predictive natriuretic equation accounting for estimated GFR, serum and urine creatinine, and half-life of the diuretic used, allowing detection of an inadequate diuretic response early in the ADHF trajectory [19]. This equation has been validated in a larger patient cohort and has been integrated into a nurse-directed protocol, resulting in increased urine output and weight loss [20].

The Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) trial compared a diuretic strategy guided by spot urinary sodium measured 2 h after and urine output measured within 6 h of diuretic administration (where presence of both a spot urinary sodium > 50 mEq/L and urine output > 100 mL/h was defined as a good diuretic response) to standard of care in 401 patients hospitalized with ADHF. In this study, the natriuresis-guided strategy led to greater natriuresis and diuresis with reduced lengths of stay (5.8 vs. 7 days) [21]. Similarly, the Pragmatic Urinary Sodium-based algorithm in Acute Heart Failure (PUSH-AHF) trial randomized 310 patients with ADHF to a natriuresis-guided strategy or standard of care [22]. Urine sodium and output were measured at defined timepoints between 2 and 36 h. If urinary sodium (≤ 70 mEq/L) or urine output (≤ 150 mL/h) was insufficient, decongestive therapy was adjusted based on a standardized protocol, provided the patient was still volume overloaded. While the primary

Table 2 Pharmacokinetics of diuretics

Diuretic	Renal site of action	Bioavailability	Usual/equivalent* oral dose	Usual/equivalent* IV dose	Elimination half-life, hours		
	Proximal tubule				Normal	HF	CKD
Acetazolamide	Inhibits carbonic anhydrase	85–90%	250–500 mg daily	250–500 mg daily	3–9	↔	↑
Dapagliflozin	Inhibits SGLT-2	78%	10 mg daily	-	12.9	↔	↑
Empagliflozin	Inhibits SGLT-2	?	10 mg daily	-	12.4	↔	↑
Sotagliflozin	Inhibits SGLT-1 and SGLT-2	25%	200–400 mg once daily	-	21–35	↔	↑
Loop of Henle							
Furosemide	Inhibits NKCC	50–60%	20–80 mg 1–2 times daily 80 mg*	40–160 mg 1–3 times daily 40 mg*	1.5–2	2.7	2.6–2.8
Bumetanide	Inhibits NKCC	80–100%	0.5–2 mg 1–2 times daily 1 mg*	0.5 to 4 mg 1–3 times daily 1 mg*	1	1.3	1.6
Torsemide	Inhibits NKCC	68–100%	10–40 mg once daily 20 mg*	N/A	3–4	6	4–5
Distal tubule							
HCTZ	NCC	65–75%	25–50 mg once daily	N/A	6–15	↔	↑
Chlorthalidone	NCC	60–72%	25–50 mg once daily	N/A	40–60	↔	↑
Chlorothiazide	NCC	-	N/A	250–1000 mg 1–2 times daily	1–2		
Metolazone	NCC	65–90%	2.5–5 mg 1–2 times daily	N/A	14–20	↔	↑
Distal tubule							
Spironolactone (steroid)	Inhibits mineralocorticoid receptor	> 90%	25–50 mg once daily	N/A	< 2 Active metabolites > 12–24	?	↑
Eplerenone (steroid)	Inhibits mineralocorticoid receptor	70%	50–100 mg once daily	N/A	4–6	?	?
Finerenone (non-steroid)	Inhibits mineralocorticoid receptor	44%	10–20 mg once daily	-	2–3	↔	↔
Amiloride	ENaC	50%	5–10 mg 1–2 times daily	N/A	6–9	?	↑
Triamterene	ENaC	52–80%	100 mg twice daily	N/A	2–5	?	↔
Collecting Duct							
Tolvaptan	V2 receptor	42–80%	60–120 mg daily as divided doses	N/A	3–12	↑	?

Adapted from references: 4, 6, 8, 9, 10, 11. *CKD*, chronic kidney disease; *HF*, heart failure; *ENaC*, epithelial sodium channel; *IV*, intravenous; *NCC*, sodium-chloride co-transporter; *NKCC*, sodium–potassium-2-chloride co-transporter; *V2*, *SGLT*-2, sodium-glucose cotransporter-2; *V2*, vasopressin receptor 2. *Equivalent doses to oral furosemide; torsemide to furosemide conversion based on [9]

endpoint of 24-h natriuresis was significantly higher in the natriuresis-guided group, all-cause mortality or HF rehospitalization at 180 days did not differ between the two groups.

The use of spot urine sodium to assess diuretic response is included in the European HF guidelines [23]. Yet, this approach has potential limitations. Variability in timing of urine collection, hydration status, and dietary sodium intake can affect spot urinary sodium levels. Additionally, studies

evaluating this approach have assessed response within the first few days of hospitalization and the efficacy of this approach in patients with acute kidney injury, critical illness, or prolonged lengths of stay has not been evaluated [4, 24]. Finally, while spot urinary sodium may provide a personalized approach to diuretic therapy by early identification of diuretic resistance, its clinical adoption has been limited by logistic challenges such as the need for standardized timed urine collection [24, 25].

Table 3 Summary of major decongestive trials

CLOROTIC	ADVOR	ENACT-HF	PUSH-AHF	DICTATE-AHF	EVEREST	ATHENA-HF	ROSE-AHF	DOSE
-Hospitalized with ADHF -On oral loop diuretic for a month	-Hospitalized with ADHF -Signs of vol. overload -Elevated natriuretic peptides -On oral loop diuretic for a month	-Hospitalized with ADHF -Signs of vol. overload -Elevated natriuretic peptides -On oral loop diuretic for a month	-Hospitalized with ADHF -No ejection fraction or natriuretic peptide inclusion or exclusion criteria	-Hospitalized with ADHF -71% with T2DM -eGFR ≥ 25 mL/min/1.73 m ² -Treatment with IV diuretic	-Hospitalized with ADHF -NYHA class 3–4 symptoms -HF-rEF $\leq 40\%$ -Hospitalized no more than 48 h earlier	-Hospitalized with ADHF -Signs of vol. overload -Elevated natriuretic peptides	-Hospitalized with ADHF -eGFR 15–60 mL/min/1.73 m ²	-Hospitalized with ADHF -On oral loop diuretic for a month
HCTZ or placebo	Acetazolamide or placebo	Standard of care or standardized natriuresis-guided diuretic protocol	Natriuresis guided arm vs. standard of care	Dapagliflozin or protocolized care	Tolvaptan vs. placebo	High-dose spironolactone vs. placebo or low-dose spironolactone	Low dose IV dopamine vs. placebo	Low dose vs. high dose, bolus vs. continuous infusion IV furosemide
35%	43%	56%	16% HFpEF	52%	100%	73% (LVEF < 45%)	81% (LVEF < 50%)	33–36 (± 17 –18)
80–240 mg	40 mg (40–60)	40 mg	80 mg	Pre-randomization 80 mg IV furosemide (40–160)	No data but 97% on diuretics at baseline	80 mg (40–160)	80 mg (range 40–160)	80–240 mg
43 (32–58)	39 (29–52)	49 (32–74)	53 (35–73)	Treat: 51 (43–68) Cont: 54 (40–71)	No data, 27% had CKD	Treat: 55 (46–71) Cont: 58 (45–75)	Treat: 46 (31–59) Cont: 45 (33–53)	Creatinine 1.5 $\pm$ 0.5 mg/dL
Weight loss/40 mg furosemide @ 72 h increased with HCTZ but no difference in patient-reported dyspnea	Congestion score within 72 h improved with acetazolamide	Natriuresis after 1 day was higher in the protocolized group Natriuresis and diuresis after 2 days was greater in the protocolized group No differences in weight loss and congestion score	Natriuresis after day 1 was higher in the natriuresis guided group Natriuresis and diuresis after 2 days was greater in the natriuresis guided group	No significant change in diuretic efficiency @ 5 days	Improved dyspnea and reduced body weight @ 24 h with tolvaptan	No significant difference in log NT-proBNP reduction or kidney function @ 96 h	No difference in cumulative urine volume, cystatin C, urinary sodium, and weight @ 72 h	Change in weight, net fluid loss, and increase in serum creatinine > 0.3 mg/dL @ 72 h Higher with high dose IV furosemide No change with continuous vs. bolus IV furosemide
No difference in hospital length of stay, all-cause mortality, and all-cause hospitalizations @ 30 and 90 days	No difference in all-cause death or rehospitalization for HF @ 3 months	No difference in in-hospital mortality	No difference in 180-day HF rehospitalization or all-cause mortality	No difference in inpatient worsening HF and 30-day readmission for HF or diabetes-related issues	No difference in all-cause mortality or composite of HF hospitalizations and cardiovascular death	No difference in 30-day all-cause mortality or HF hospitalization	No differences in death, days alive, and free from HF hospitalization @ 60 days	No difference in composite of death, rehospitalization, or emergency department visits @ 60 days
54–56%	52%	67%	55%	52%	84%	60%	50%	64%
54–67%	81%	79%	69%	59%	70%	74%	83%	83%
32–37%	42%	52%	35%	51%	54%	11%	30%	28%

ACEi, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; HF-rEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal brain natriuretic peptide. References: 8, 21, 22, 26, 29, 30, 33, 36, 40, 62

Table 4 Strategies for assessing diuretic response

Strategies for assessing diuretic response	Advantages	Limitations
Weight monitoring	-Easy to obtain if patient factors and logistics are in order	-Not consistently performed -limited by mobility/bed weights -Dry weights can change based on changes in visceral body mass
Urine output monitoring	-Easy to obtain if patient factors and logistics are in order	-Not consistently and accurately performed -Limited by patient factors such as mobility and incontinence
Spot urine sodium	-Consistent and easy to use or compare -Can detect early diuretic responsiveness/resistance -Can be part of nurse driven protocols	-Logistics might be difficult with unit staffing and work needed -Inconsistent/different cutoffs -Can be influenced by tubular dysfunction/AKI -Not tested in patients with prolonged diuresis/hospital stays or critical illness
Spot urine sodium with natriuretic equation	-More accurate since considers existing kidney function and diuretic half-life	-Utilized mainly bumetanide -Complex given calculations needed even with online calculator availability -Similar limitations as with spot urine sodium above
BAN-ADHF prediction model and other risk prediction models	-Can help anticipate patients who will develop diuretic resistance	-Mainly predicts diuretic resistance rather than measuring diuretic response
Commonly used lab parameters such as BUN, serum creatinine response, hematocrit, bicarbonate, natriuretic peptides	-Routinely available -Can provide clues in relation to volume status	-Do not measure diuretic response directly but may reflect volume status -Nonspecific and affected by co-morbid medical conditions

AKI, acute kidney injury; CKD, chronic kidney disease. *Limitations may vary depending on institution and clinical setting. References: 6, 19, 20, 21, 23, 24, 78

Medical strategies to overcome diuretic resistance

Carbonic anhydrase inhibition

Acetazolamide is a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption [26]. In the Acetazolamide in Acute Heart Failure with Volume Overload (ADVOR) trial of 519 patients with ADHF, randomized to either acetazolamide (500 mg IV once daily) or placebo in addition to IV loop diuretics, successful decongestion, defined as absence of signs of volume overload within 3 days after randomization and no indication for escalation of decongestive therapy, was significantly higher in the acetazolamide group compared to placebo (42.2% vs. 30.5%; RR 1.46; 95% CI 1.17–1.82) [26]. Acetazolamide resulted in greater natriuresis, diuresis, and shorter lengths of stay. However, all-cause mortality or HF re-hospitalizations at 3 months did not differ between the 2 groups [26]. There was no statistical difference in adverse events including metabolic acidosis, hypokalemia, hypotension, or renal dysfunction between the 2 groups. Limitations of this study were that it utilized a clinical decongestion score and did not report weight loss. Variability in urine collection methods and the ability to augment diuresis with other agents also

complicated assessment of the trial results. Acetazolamide was found to be more effective in patients on lower doses of maintenance diuretics (<60 mg/day) and thus its efficacy in diuretic-resistant patients remains unclear. Lastly, sodium-glucose co-transporter 2 inhibitor (SGLT-2i) use was excluded in this trial and the utility and safety of acetazolamide in the current era where most patients should be treated with SGLT-2i remains unclear [26].

SGLT2 inhibition

SGLT2i inhibits glucose and sodium uptake (approximately 5%) in the proximal tubules, thus promoting osmotic diuresis and natriuresis [26]. The first small RCT (EMPA-RESPONSE-AHF, $n = 80$) that evaluated the utility of empagliflozin in patients hospitalized with ADHF found that even though there was a significant increase in urine output with SGLT2i, there was no difference in dyspnea score, weight change/40 mg of furosemide, or NT-proBNP levels. However, the combined endpoint of in-hospital worsening HF, rehospitalization, or death at 60 days was reduced compared to placebo [27]. Similar results were observed in the Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients with Acute Decompensated Heart Failure (EMPAG-HF, $n = 60$) trial, where

empagliflozin use was associated with increased urine output and diuretic efficiency and decreased NT-proBNP levels after 5 days of treatment relative to placebo. No significant differences were seen in 30-day mortality [28]. In the Impact of Empagliflozin on Decongestion in Acute Heart Failure (EMPULSE) trial, a double-blind placebo-controlled randomized trial of 530 patients with ADHF, patients treated with empagliflozin demonstrated a greater improvement in markers of decongestion including weight loss adjusted for mean daily diuretic dose, NT-proBNP, hematocrit, and clinical decongestion score [29]. The primary endpoint defined by a hierarchical composite win ratio of death, number of HF exacerbations, time to first HF exacerbation, and change from baseline in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) 90 days after randomization showed clinical benefit with empagliflozin (stratified win ratio, 1.36; 95% CI 1.09–1.68) [29]. Although this trial excluded patients with eGFR < 20 mL/min/1.73 m², approximately one-third had eGFR < 45 mL/min/1.73 m² reflecting more advanced stages of CKD. While empagliflozin use was associated with an expected dip in eGFR within the first 2 weeks, renal function returned to baseline over the 90-day follow-up period.

The recent randomized, open-label Efficacy and Safety of Dapagliflozin in Acute Heart Failure (DICTATE-AHF) trial examined whether dapagliflozin 10 mg daily vs. protocolized diuretic treatment alone improved diuretic efficiency in 240 patients with ADHF. While dapagliflozin did not improve diuretic efficiency, it increased 24-h urine output and natriuresis and expedited hospital discharge without adversely affecting renal function. There was also lower net loop diuretic dose use in the dapagliflozin group compared to placebo [30].

Differences between the observed effects of SGLT-2i on diuretic efficiency in the EMPULSE vs. DICTATE-HF trials may relate to the timing of SGLT-2i initiation (after initial stabilization in EMPULSE vs. within 24 h of admission in DICTATE-HF) and the use of protocolized diuretic up-titration in DICTATE-HF vs. usual care in EMPULSE. In sum, these trials demonstrate that SGLT-2i promotes decongestion in ADHF while reducing HF admissions and cardiovascular mortality. However, across trials involving SGLT2i and diuresis, although there was a consistent increase in urinary volume, there was no significant change in urinary sodium excretion, and their diuretic effect was not sustained [31]. Furthermore, the benefits of SGLT-2i on cardiovascular outcomes appear to be mediated primarily by mechanisms that provide cardioprotection rather than direct decongestion [31].

Thiazide diuretics

Thiazide diuretics inhibit the sodium chloride cotransporter (NCC) in the distal convoluted tubule, which reabsorbs approximately 7% of filtered sodium [32]. As mentioned above, chronic diuretic use can lead to remodeling and hypertrophy in the distal tubule and collecting duct, causing diuretic resistance [4]. To address this, sequential nephron blockade with thiazide diuretics has classically been used to augment diuresis by blocking downstream sodium reabsorption from the loop of Henle [4]. In the Combining Loop with Thiazide Diuretics for Decompensated Heart Failure (CLOROTIC) trial, 230 patients were randomized to receive hydrochlorothiazide or placebo in addition to furosemide [33]. Patients on hydrochlorothiazide lost more weight at 72 h (2.3 vs. 1.5 kg) and had greater 24-h diuresis and weight loss/40 mg of furosemide [33]. Although the CLOROTIC trial enrolled patients with higher baseline diuretic requirements (≥ 80 mg furosemide daily) and adjusted thiazide dose for baseline renal function, the trial was terminated prematurely for slow enrollment. This raises concerns about adequate power to detect outcomes. Additionally, there were higher rates of electrolyte abnormalities and renal dysfunction with no significant differences in rehospitalization and mortality [33]. Metolazone, another thiazide like diuretic, has also been studied for ADHF. A meta-analysis ($n=334$ patients) comparing metolazone plus furosemide vs. furosemide alone showed a higher 24-h total urine volume with metolazone (mean difference 692.70, 95% CI 386.59 to 998.82) [34]. A small ($n=60$) double-blind randomized study compared oral metolazone, IV chlorothiazide, or tolvaptan therapy in addition to IV furosemide in patients with ADHF and diuretic resistance [35]. All 3 interventions significantly improved diuretic efficiency without significant differences in weight loss [35]. Overall, combination thiazide diuretic therapy seems effective in promoting diuresis, but concerns remain about electrolyte abnormalities, renal function, and impact on hard outcomes.

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists (MRA) exert their diuretic effects via competitive inhibition of aldosterone receptors in the distal convoluted tubule. The Efficacy and Safety of Spironolactone in Acute Heart Failure (ATHENA-HF), which randomized 360 patients with ADHF, found no significant differences in outcomes between high-dose spironolactone (100 mg) vs. low-dose spironolactone (25 mg) or placebo. There were no significant changes in NT-proBNP levels, time

to first HF readmission, or mortality [36]. Net urine output, weight change, and requirement for loop diuretics were also similar between groups [36]. Spironolactone's slower mechanism of action (prodrug needing conversion to its active metabolite canrenone) and the study's lack of focus on patients with worse renal function or diuretic resistance may explain these findings [36]. In contrast, in a smaller non-randomized study ($n=20$ per group) of diuretic-resistant patients, high-dose spironolactone (up to 200 mg/day if weight loss <0.5 kg per day), administered with patiromer (if K^+ >4.3 mmol/L), led to clinically important weight loss and reduced dyspnea. However, given the small sample size, these findings need further validation [37]. Overall, the evidence for sequential nephron blockade with MRAs remains limited.

Finerenone, a non-steroidal MRA, has been shown to reduce HF hospitalizations and slow the progression of CKD in patients with type 2 diabetes and CKD [38]. More recently, the FINEARTS-HF trial demonstrated that finerenone also reduces HF hospitalizations in symptomatic HF patients with LVEF $\geq 40\%$, many of whom were either admitted with ADHF or were recently discharged after diuresis [39]. Finerenone and other non-steroidal MRAs may hold promise for the prevention or treatment of diuretic resistance in patients with ADHF and require further study.

Vasopressin antagonists

Tolvaptan inhibits vasopressin (V2) receptors in the collecting duct and promotes decongestion by increasing the excretion of free water. The Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure (EVEREST) trial randomized 4133 patients with ADHF to tolvaptan (30 mg daily) or placebo [40]. Tolvaptan had no effect on long-term mortality but did improve dyspnea, body weight, and edema [40]. The Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure (TACTICS-HF) trial randomized 257 patients with ADHF to tolvaptan (30 mg given at 0, 24, and 48 h) or placebo, in addition to furosemide. Tolvaptan led to greater fluid and volume loss but did not improve the proportion of patients having significant improvement in dyspnea without the need for additional therapy or death [41]. The Short-Term Effects of Tolvaptan in Patients with Acute Heart Failure and Volume Overload (SECRET of CHF) trial, which focused on patients with diuretic resistance (urine output ≤ 125 mL/h following IV furosemide ≥ 40 mg) and renal dysfunction ($eGFR < 60$ mL/min/1.73 m²), showed that tolvaptan led to greater weight reduction but did not significantly affect the primary endpoint of dyspnea relief [42]. Lastly, a meta-analysis of 5000 patients, primarily driven by

the EVEREST trial, showed that short-term use of tolvaptan in hospitalized patients with ADHF improved dyspnea, reduced body weight, improved edema, and increased urine output without increasing mortality [43]. While evidence for tolvaptan's impact on hard outcomes remains limited, it appears to be effective in promoting decongestion. As with any treatment, the potential risks and benefits of tolvaptan need to be carefully balanced.

Other strategies

Albumin

Hypoalbuminemia is hypothesized to play a role in diuretic resistance by increasing the volume of distribution of loop diuretics, thereby hindering their secretion and action on renal tubule transporters [4]. The putative rationale for using albumin as decongestive therapy is to enhance the plasma refill rate, driven by colloidal osmotic pressure [44, 45], and to mobilize redistributed volume into the vascular space [46]. However, there are conflicting data regarding the role of albumin. A recent single-center analysis showed that serum albumin levels were not associated with urinary diuretic excretion and urinary albumin levels were not linked to diuretic efficiency [47]. Similarly, an analysis of the DOSE-AHF and Renal Evaluation Strategies in Acute Heart Failure (ROSE-AHF) trials showed that baseline serum albumin levels were not associated with worsening HF, worsening kidney function, or freedom from congestion [48]. Conversely, a meta-analysis including 13 studies with 400 patients revealed that co-administration of furosemide and albumin increased natriuresis and diuresis, especially in patients with albumin levels <2.5 g/dL [49], with the limitation that the included studies had small sample sizes, small treatment effects, and high heterogeneity. Overall, the evidence for albumin use in HF remains inconsistent and requires further exploration.

Hypertonic saline and chloride supplementation

Hypertonic saline has been studied in ADHF to facilitate redistribution of fluid into the intravascular compartment, with subsequent plasma expansion leading to reduced neurohormonal activation and systemic vascular resistance [50]. It is also postulated that sodium and chloride supplementation may help counteract the strong renal anti-diuretic neurohormonal response that is seen in patients

with ADHF [50, 51]. Short-term effects of hypertonic saline solution in ADHF and long-term effects of moderate sodium restriction in patients with compensated New York Heart Association class III HF were studied in the SMAC-HF study [52]. This single-blinded study randomized 1771 patients with ADHF to IV furosemide plus hypertonic saline (150 mL of 1.4–4.6% NaCl) twice daily and moderate sodium restriction (120 mmol) vs. IV furosemide twice daily without hypertonic saline and a low sodium diet (80 mmol) [52]. The study demonstrated higher rates of diuresis, reduced lengths of stay, and lower rates of readmissions (18.5% vs. 34.2%) and mortality (12.9% vs. 23.8%) with hypertonic saline [52]. A recent meta-analysis of 10 trials with 3000 patients showed that co-administration of hypertonic saline with furosemide significantly increased urine output (MD 528.57 mL/24 h; 95% CI 431.90 to 625.23) and urine sodium (MD 54.85 mmol/24 h; 95% CI 46.31 to 63.38) and reduced serum creatinine and length of stay [53]. However, a recent multicenter randomized double-blind trial of 168 outpatients with worsening symptoms of congestion compared a single dose of IV furosemide to IV furosemide plus hypertonic saline administration tailored to serum sodium levels and showed no significant differences in diuresis and natriuresis after 3 h [54]. This study was limited by its use of a fixed loop diuretic dose (less than twice the home dose) and the short duration of monitoring (within 3 h) for acute outcomes [54]. Therefore, use of hypertonic saline has not gained traction due to conflicting evidence regarding its efficacy and the seeming contradiction between its use and the pathophysiology of HF [51].

Chloride plays a major role in sodium regulation and mediates tubuloglomerular feedback and renin release in the kidney [51, 55]. Post hoc analyses of ROSE-AHF [56] and placebo-controlled randomized study of the selective A1 adenosine receptor antagonist KW-3902 for patients hospitalized with acute HF and volume overload to assess Treatment Effect on Congestion and renal function Trial (PROTECT) [57] trials have shown that low baseline chloride levels are associated with worse diuretic efficiency. In a small pilot study of 10 stable patients receiving ≥ 80 mg daily furosemide, supplementation with lysine chloride resulted in hemoconcentration, weight loss, reduced NT-proBNP levels, increased plasma renin activity, and increased BUN to creatinine ratio [58]. In a post hoc analysis of the ADVOR trial, hyponatremia was associated with slower decongestion, longer hospital stays, and higher risks of all-cause mortality and HF readmissions. Acetazolamide increased the odds of successful decongestion and reduced lengths of stay irrespective of serum chloride levels. Notably, in hyponatremic

patients, acetazolamide raised chloride levels and prevented further declines compared to placebo [59]. Ongoing studies are evaluating the use of chloride supplementation in acute decompensated HF (NCT03446651).

Inotropes

In cardiogenic shock, inotropes like dopamine, dobutamine, milrinone, and levosimendan can be used to improve renal perfusion and assist in decongestion [60]. Dopamine, at low doses, can selectively vasodilate and improve renal perfusion. However, in the ROSE-AHF trial, treatment with low-dose dopamine (2 mcg/kg/min) on top of the high-intensity diuretic protocol used in the DOSE trial in patients with ADHF and baseline CKD (eGFR 15–60 mL/min/1.73 m²) had no effect on 72-h urine volume or change in cystatin C [61, 62]. In a post hoc analysis, low-dose dopamine led to greater urine volume and weight reduction in patients with HF with reduced ejection fraction but not in those with HF with preserved ejection fraction [61]. In general, trial data do not support the use of dopamine due to lack of renal function improvement and the potential for tachyarrhythmias [60]. Dobutamine has demonstrated increased renal plasma flow and GFR in small studies [63] but did not demonstrate favorable outcomes in larger trials with a signal towards higher mortality [60]. Milrinone has been associated with higher renal oxygenation and renal blood flow in patients undergoing cardiac bypass surgery [64]. However, a sub-analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) showed that while milrinone led to improvements in renal function, and there was no difference in hard clinical outcomes [65]. Lastly, levosimendan, a calcium sensitizing inotrope and vasodilating agent, was associated with greater weight loss and less worsening renal function in an observational study of 96 patients with ADHF and CKD (eGFR < 60 mL/min/1.73 m²) [66]. However, larger trials failed to show consistent improvement in kidney or clinical outcomes and levosimendan use was associated with higher rates of hypotension, arrhythmias, and death [67–69]. Despite the lack of mortality benefit, signals for improved kidney outcomes and decongestion make inotropes a valuable option for the management of patients with severe ADHF or cardiogenic shock.

Ultrafiltration

The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial compared early ultrafiltration to IV diuretics in 200 patients with ADHF and found greater

weight and fluid loss with ultrafiltration [70]. However, the Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome (CARRESS-HF) trial which compared fixed rate ultrafiltration to diuretic therapy in patients with ADHF and worsening renal function showed an increase in serum creatinine levels and no significant difference in weight loss with ultrafiltration, along with increased bleeding and catheter-related complications [71]. The Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) trial, comparing adjustable ultrafiltration to IV diuretics, found fewer HF and cardiovascular events with ultrafiltration [72]. However, this trial was stopped prematurely by the study sponsor [72]. A recent meta-analysis of 10 RCTs with 900 patients showed that ultrafiltration reduced HF hospitalizations (risk ratio 0.72; 95% confidence interval [0.55–0.96]) but failed to show improvements in other outcomes due to significant heterogeneity. It also lacked an analysis of overall adverse events [73]. Peritoneal ultrafiltration is a possible alternative, with a recent meta-analysis of 769 patients showing improved NYHA functional class and shorter hospital stays. However, high heterogeneity and risk of bias limit these findings [74]. Ultrafiltration may be beneficial in decongesting patients with ADHF and diuretic resistance but uncertainty remains regarding its risk–benefit ratio and the optimal timing of ultrafiltration due to the lack of adequately powered and standardized studies.

Limitations of current decongestive strategies

Enhanced decongestive strategies in ADHF have not consistently improved long-term outcomes, partly because short-term interventions may not produce lasting effects. Inconsistent study results may also reflect differences in patient populations, such as baseline diuretic use and kidney function. Notably, trials like ADVOR and CLOROTIC have often excluded patients with advanced CKD (stages 4 and 5) (Table 3) who are at the highest risk for diuretic resistance and persistent congestion. Most studies on enhanced decongestive approaches focus on short-term diuretic response (48–72 h), which can help identify or prevent early-phase diuretic resistance but does not address patients who develop resistance or persistent congestion later in treatment. Moreover, while enhanced decongestive strategies or combined diuretic approaches may be more effective initially, they carry higher risks of side effects like electrolyte imbalances. Single loop diuretic therapy, although simpler, may lead to downstream nephron adaptation leading to resistance

[4], highlighting the trade-off between efficacy and safety in managing decongestion.

Another component that needs attention is the sodium avidity driven by neurohormonal upregulation and mechanisms to counter this response. Contemporary studies reveal that only 50–70% of patients with relatively preserved kidney function are on ACEi/ARB/ARNI therapy (Table 3) [21, 22], despite strong evidence for GDMT improving HF outcomes [75] and the safety of rapid up-titration of GDMT in ADHF patients [76]. In a study of 103 ADHF patients, those with urine sodium < 60 mEq/L had lower admission blood pressures, less chronic use of neurohormonal antagonists, and worse outcomes at 90 days [77].

While GDMT optimization does not replace the need for adequate decongestion, optimizing GDMT during the acute HF hospitalization can improve clinical outcomes and may reduce diuresis-related risks like hypokalemia [78]. However, in patients with advanced CKD, caution is needed when up-titrating GDMT alongside decongestion due to risks of hyperkalemia and hypotension. Notably, the STRONG-HF trial on rapid up-titration of GDMT, excluded patients with eGFR < 30 mL/min/1.73 m² [68]. Thus, in patients with ADHF, the goal should be to achieve both effective decongestion and optimize GDMT.

Future directions

To improve the treatment of diuretic resistance, clinical trials should focus on early and accurate identification of at-risk patients, including more high-risk groups. While single biomarkers like urine sodium have limitations, combining multiple markers and dynamic patient data could enhance prediction, particularly through machine learning and artificial intelligence. For example, machine learning applied to data from trials like ROSE-AHF, CARRESS-HF, and ATHENA-HF led to the development of the BAN-ADHF score, which uses clinical variables, such as kidney function, blood pressure, home diuretic dose, natriuretic peptides, and comorbidities, to predict diuretic efficiency [79]. This score showed high predictive performance when externally validated in different study populations including the DOSE/ESCAPE cohorts and GWTHG-HF registry. Another machine learning model analyzing data from approximately 18,000 Chinese patients demonstrated high accuracy (AUC 0.95) by integrating comprehensive metabolic and complete blood count parameters along with natriuretic peptides [80]. Integrating such models into the electronic medical record could streamline early identification of patients at risk for diuretic resistance [81].

Table 5 Novel diuretics and mechanisms

Novel Diuretic	Mechanism
Urea transport inhibitors	Inhibit urea transporters in the tubular epithelial cells (UT-A) and in vasa recta endothelia (UT-B) to disrupt urinary concentrating ability and promote salt sparing diuresis
ROMK inhibitors	Inhibition of ROMK in the thick ascending loop of Henle reduces luminal potassium efflux, thus reducing sodium reabsorption by NKCC Inhibition of ROMK in the cortical collecting duct reduces potassium secretion, thus reducing sodium uptake by ENaC
WNK/SPAK/OSR1 inhibitors	Inhibition of the WNK signaling cascade reduces phosphorylation and activation of NKCC and NCC, reducing sodium reabsorption by these channels
Pendrin inhibitors	Inhibition of pendrin, a Cl ⁻ /HCO ₃ ⁻ exchanger in the distal nephron, reduces Cl ⁻ reabsorption and consequently sodium reabsorption in the distal nephron

ENaC, epithelial sodium channel; *GFR*, glomerular filtration rate; *NCC*, sodium-chloride cotransporter; *NKCC*, sodium-potassium-2-chloride cotransporter; *OSR1*, oxidative stress-responsive 1; *ROMK*, renal outer medullary potassium channel; *SPAK*, STE20/SPS1-related proline/alanine-rich kinase; *UT-A/B*, urea transporter A/B; *WNK*, lysine deficient protein kinase. Reference: 81

Head-to-head comparisons of enhanced decongestive strategies and studies evaluating combinations of agents targeting different segments of the nephron are needed. For instance, the Diuretic Treatment in Acute Heart Failure with Volume Overload Guided by Serial Spot Urine Sodium Assessment (DECONGEST) trial (NCT05411991) will evaluate spot urine sodium guided diuresis in ADHF, utilizing upfront acetazolamide and chlorthalidone, with IV canrenoate (aldosterone antagonist) added for cases of diuretic resistance. Additionally, novel diuretic agents, such as non-steroidal MRAs, inhibitors of the WNK serine threonine kinase and its downstream kinase substrates SPAK (SPS-1 related proline/alanine rich kinase) and OSR1 (oxidative stress-responsive kinase 1), pendrin inhibitors, and inhibitors of urea transporter proteins warrant further study [11] (Table 5) [82]. Device therapies that can reduce

afterload, reduce venous congestion, increase cardiac output, and facilitate diuresis [78] may also hold promise, particularly for critically ill patients.

Finally, standardized measures for monitoring and assessing decongestion in the real-world setting are essential. Objective biomarkers, like adrenomedullin, studied in the STRONG-HF trial, show promise for predicting congestion and outcomes [83]. Combining static and dynamic variables with machine learning may enhance assessment of congestion status and risk for diuretic resistance. Additionally, greater utilization of remote monitoring devices, such as implantable hemodynamic monitors and point of care ultrasound protocols (e.g., VEXUS) assessing hepatic and kidney venous flows [4], could further support assessment of congestion (see Table 6 for summary of gaps).

Table 6 Potential gaps in knowledge

1	There is no universal definition of diuretic resistance
2	There are inadequate trials on decongestion in patients with diuretic resistance
3	There are limited head-to-head trials comparing strategies of enhanced decongestion (SGLT2i vs. acetazolamide vs. thiazide) or combinations of multiple strategies
4	There is lack of data showing whether early initiation of enhanced decongestive therapy (SGLT2i/acetazolamide/thiazide) at the onset of heart failure admission leads to less downstream diuretic resistance and improved clinical outcomes
5	There is a lack of data regarding patient selection, timing of use, and clinical outcomes with advanced mechanical decongestive devices
6	While spot urine sodium can predict early diuretic response, there are inadequate data to evaluate whether the cut-offs need to be adjusted over time and with different diuretic regimens
7	There is a lack of studies on deliberate early optimization of GDMT/neurohormonal blockade to help prevent diuretic resistance and enhance decongestion
8	There is inadequate data on decongestion and interpretation of changes in kidney function in the setting of critical illness, inotropic support, and mechanical circulatory support
9	There is no single reliable biomarker or non-invasive method for accurately measuring residual congestion or volume status
10	There is lack of standardization in the use of common measures of decongestion and criteria for discharge

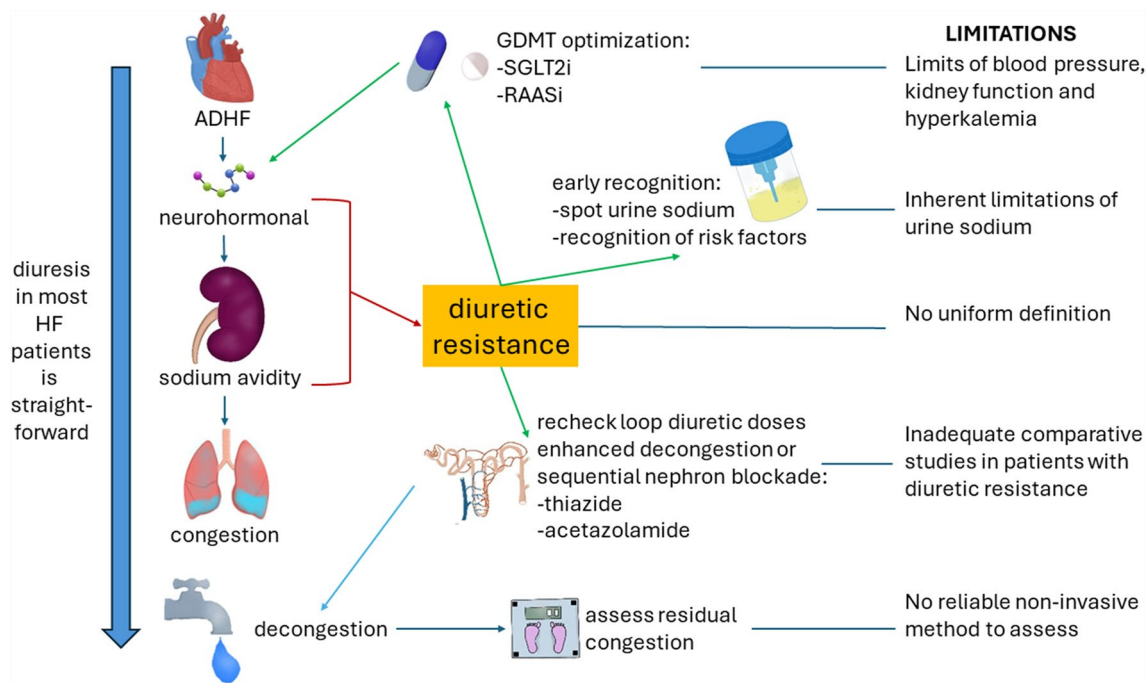


Fig. 1 Summary figure

Summary

Optimizing GDMT and achieving adequate decongestion are crucial to improving outcomes in HF. However, diuretic resistance remains a challenge in ADHF management, underscoring the need for further research in this area. While strategies to overcome diuretic resistance have shown promise in increasing early urine output and sodium excretion in clinical trials, only SGLT-2i has significantly impacted hard outcomes (Fig. 1).

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Declarations

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